

III. REMARKS

Claim Status

Claims 1-6, 9 and 11-14 are active in the case and stand rejected.

Claim Rejections - 35 USC § 103

Claims 1, 4-6, 9, 11, and 14 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Salahshor et al. (1999, previously cited), Davies et al. (June 2002, previously cited), Kmiec et al. (W0200173002 published 2001, previously cited), Shuber et al. (W0200118252 published 2001, previously cited), Ferrie et al. (GB2327497 published 1999, previously cited), Coste et al. (1998, previously cited), Nollet et al. (1996, previously cited), Albertsen et al. (United States Patent 6,114,124 issued 2000, previously cited), Ikawa et al. (1988, previously cited), McCormick (1999), Buck et al. (1999, previously cited), and Stratagene (1988).

The examiner's extensive analysis of the prior art and its applicability to applicant's claims has previously been noted. In opposition to the examiner's conclusions applicant submits the Declaration of Pablo Steinberg, one of the inventors hereof which definitively refutes the examiner's conclusions.

The examiner, in applicant's previous response found applicant's attorney's arguments not to be persuasive, but buttressed as they now with the technical points made by Dr. Steinberg in his Declaration are expected to now persuade the examiner as to the non-obviousness of the instant invention.

Applicant has previously amended the claims to more clearly denote that it is not the identity of the individual genes or gene fragments that is the crux of applicant's invention but rather that it is the combination of specifically

claimed components that solves the problems in the prior art as recited in paragraphs [0005] to [0011] of applicant's published application.

The claimed method yields the improved results as recited in the specification at paragraphs [0012] and [0025] to [0027]; results which were not previously obtainable.

Among the advantages previously stated to be unobtainable but now obtainable utilizing the claimed method are:

1. a single test
2. non-invasive
3. uses 2 signal pathways
4. allows detection of previously unknown mutations within regions where mutations occur more frequently
5. inexpensive and simple enough to be part of routine examinations
6. not limited to a few point mutations
7. useful in automated testing
8. diagnoses colon cancer at an early stage

After extensive analysis, the examiner concludes that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the methods of the methods of the prior art with a reasonable expectation of success. But as shown in Dr. Steinberg's Declaration it is not as easy as that. The multiplicity of pathways and of markers put finding the right combination beyond the reach of the practitioner skilled in the relevant art.

The examiner states that the motivation to do so is provided by the multiplicity of prior art references cited, each of which provides a provides a bit of information which if combined in a specific way, allegedly add up to making applicant's invention obvious. The examiner's position is definitely refuted by Dr. Steinberg's Declaration.

At paragraphs 11 and 12 of his Declaration Dr. Steinberg effectively distinguishes the Salahshor et al. and Davies et al. references.

"11. For example Salahshor et al. (Genes Chromosomes and Cancer, Volume 26, Number 3, November 1999, pages 247-252; document cited by the Examiner) show the frequency of mutations of the genes APC, K-Ras, TP53 and TGF β R2 in MSI-H tumors. The mutation frequency was 86,4% for TGF β R2 and between 4% and 23% for the others. In view of MSS tumors no TGF β R2 mutations were found but a 35%, 57% and 60% frequency of mutations in cases of K-Ras, APC and TP53. A total detection rate of the analyzed carcinomas was not published.

12. Davies et al. defined the gene marker B-Raf, which mutated in 86% of melanomas (Nature, Vol. 418, Number 20, August 2002, pages 949-954; also a cited document by the Examiner). However, this gene marker showed in colon carcinomas only a 15% mutation frequency."

This highlights the fact that not only is the choice of pathway and of maker within that pathway important but he marker must be a gene marker appearing in colon carcinomas with a high mutation frequency.

The examiner has previously quoted *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), in which the Court of Appeals for the Federal Circuit determined that the existence of a general

method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

What the court goes on to say, however, is contrary to the examiners position. In the paragraph immediately following the excerpt quoted by the examiner, the court states:

"In all of these cases, however, the prior art teaches a specific, structurally-definable compound and the question becomes whether the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention."

Here, there exists nothing in the prior art that suggests making the specific modifications and combinations necessary to achieve the claimed invention.

The examiner states that the since the claimed primers simply represent structural homologs, which are derived from

sequences suggested by the prior art as useful for primers of the amplification of genes associated with colorectal cancer and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties.

This is a reiteration of the PTO position rejected by the Deuel court:

"The PTO's theory that one might have been motivated to try to do what Deuel in fact accomplished amounts to speculation and an impermissible hindsight reconstruction of the claimed invention. It also ignores the fact that claims 5 and 7 are limited to specific compounds, and any motivation that existed was a general one, to try to obtain a gene that was yet undefined and may have constituted many forms."

Thus, a *prima facie* case of obviousness has not been made and applicant respectfully requests favorable reconsideration of this ground for rejection.

Claim 2 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Salahshor et al., Davies et al., Kmiec et al., Shuber et al. (2001), Ferrie et al., Coste et al., Nollet et al., Albertsen et al., Ikawa et al., McCormick, Buck et al., and Stratagene as applied to claim 1 above, and further in view of Gerry et al. (1999).

As a *prima facie* case of obviousness has not been made out as against the independent claim, claim 1, dependent claim 2 is also not obvious.

Claim 3 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Salahshor et al., Davies et al., Kmiec et al., Shuber et al. (2001), Ferrie et al., Coste et al., Nollet et al., Albertsen et al., Ikawa et al., McCormick, Buck et al., and

Stratagene as applied to claim 1 above, and further in view of Shuber et al. (W0199858081 published 1998).

As a *prima facie* case of obviousness has not been made out as against the independent claim, claim 1, dependent claim 3 is also not obvious.

Claims 12 and 13 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Salahshor et al., Davies et al., Kmiec et al., Shuber et al. (2001), Ferrie et al., Coste et al., Nollet et al., Albertsen et al., Ikawa et al., McCormick, Buck et al., and Stratagene as applied to claim 1 above, and further in view of Baba et al. (1996).

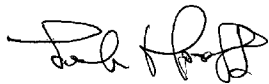
As a *prima facie* case of obviousness has not been made out as against the independent claim, claim 1, dependent claims 12 and 13 are also not obvious.

Favorable reconsideration is respectfully requested.

The Commissioner is hereby authorized to charge payment for any fees associated with this communication or credit any over payment to Deposit Account No. 14-1263.

Respectfully submitted,

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